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Original Article

Clinical manifestations of Parkinson disease and the onset of rapid eye movement sleep behavior disorder

Yan Gong [a], Kang-ping Xiong [a], Cheng-jie Mao [a], Yun Shen [a], Wei-dong Hu [a], Jun-ying Huang [a,b], Fei Han [b], Rui Chen [b], Chun-feng Liu [a,c,*]

[a] Department of Neurology, Second Affiliated Hospital of Soochow University, Suzhou, China
[b] Sleep Center, Second Affiliated Hospital of Soochow University, Suzhou, China
[c] Institute of Neuroscience, Soochow University, Suzhou, China

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ABSTRACT

Objective: To identify whether the presence and/or timing of rapid eye movement (REM) sleep behavior disorder (RBD) onset were associated with differences in clinical features and sleep parameters of Parkinson disease (PD).

Methods: In all, 112 PD patients were enrolled and all underwent extensive clinical evaluations and video-polysomnography (PSG). Clinical features and PSG parameters were compared in PD patients with (PD + RBD) or without (PD − RBD) RBD, RBD preceding (RBD > PD), or not (PD ⩾ RBD) PD onset.

Results: Sixty-three of the 112 PD patients were affected by RBD. Adjusted for age, gender, education, body mass index (BMI), levodopa equivalent daily dose (LED) and PD duration, PD + RBD patients had higher Hoehn & Yahr stage, higher scores for UPDRS parts I, II and III, more dyskinesia, higher ratio of axial/limb manifestations, and more hallucinations. Their cognitive and quality-of-life status was significantly lower (all $P < 0.05$). For PSG, PD + RBD patients exhibited higher percentages of phasic and tonic EMG activities, lower apnea hypopnea (AHI) and oxygen desaturation index (ODI), and less time in arterial oxygen saturation (SaO_2) <90% during REM sleep (all $P < 0.05$). PD ⩾ RBD ($n = 22$) patients did not significantly differ from RBD > PD ($n = 41$) patients in clinical manifestations, whereas the PD ⩾ RBD subgroup had significantly higher UPDRS part I score, lower PDQ score and lower AHI during REM than the PD − RBD group (all $P < 0.05$), but not RBD > PD subgroup. Correlation analysis showed that worse cognition was associated with shorter interval of RBD preceding PD onset ($r = 0.297$, $P = 0.018$), but not RBD duration ($P = 0.202$).

Conclusions: Clinical manifestations of PD may vary depending on the presence and timing of RBD onset. These findings are compatible with the hypothesis that RBD may be a marker of complex subtypes of PD.

1. Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by a loss of normal muscle tone during REM sleep and motor activity associated with dream content [1]. Brainstem lesions have been mainly associated with REM sleep without atonia (RWA), whereas action-filled and violent dreams are based on cortical dysfunction [2,3]. RBD constitutes an increased risk of developing neurodegenerative diseases, such as multiple system atrophy (MSA), Parkinson disease (PD), and dementia with Lewy bodies (DLB) [4].

RBD is one of most widespread non-motor symptoms of PD, but not all PD patients exhibit RBD. Moreover, RBD not only precedes or coincides with the motor symptoms of PD, but may occur during the progression of PD. According to Braak et al.'s staging system for PD [5], clinical expression with presymptomatic stages were characterized by Lewy body inclusions confined to the medulla oblongata/pontine tegmentum and olfactory bulb/anterior olfactory nucleus. These nuclei are often affected in PD prior to the involvement of the substantia nigra. This would explain why RBD precedes motor parkinsonism in PD patients. However, it does not explain why a certain proportion of PD patients does not develop RBD and why RBD may precede or develop with or after PD onset. Many studies have been performed to explore the potential

* Corresponding author at: Department of Neurology, Second Affiliated Hospital of Soochow University, 1055 Sanxiang Road, Suzhou 215004, China. Tel.: +86 512 67783307; fax: +86 512 68284303.
E-mail address: liucf@suda.edu.cn (C.-f. Liu).

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relationships between PD and RBD [6–10]. Most previous studies found that RBD was associated with longer PD duration and higher doses of dopaminergic therapy [7,10,11]. However, disease duration and medication may impact on sleep parameters and/or other clinical manifestations of PD [12]. On the other hand, the timing of RBD onset may play a role in the specificity of RBD to degenerative process of PD [13]. Nonetheless, data on the potential relationships between PD patients with RBD preceding and developing with or after PD onset are rare [11,13].

We hypothesized that RBD may be a marker of complex subtypes of PD and that PD might constitute distinct clinical and pathological subtypes related to the presence and/or timing of RBD onset. To test our hypothesis, by controlling age, gender, education, body mass index (BMI), levodopa equivalent daily dose (LED) and PD duration, we performed extensive clinical evaluations and video-polysomnography (PSG) to compare clinical features and PSG parameters in PD patients with (PD + RBD), without RBD (PD − RBD), RBD preceding (RBD > PD), or developing with or after (PD ⩾ RBD) the onset of PD.

2. Methods

2.1. Subjects

PD patients were recruited from the Center of Parkinsonism and Movement Disorders in our hospital from September 2010 to February 2013.

2.1.1. Inclusion criteria

The diagnosis of PD was established according to the UK Parkinson's Disease Society Brain Bank clinical diagnosis criteria [14].

2.1.2. Exclusion criteria

Patients with psychiatric disease or severe dementia were excluded, according to the Diagnostic and statistical manual (DSM-IV). The primary reason was that these patients were unable to co-operate with PSG or clinical tests. Patients who had taken selective serotonin reuptake inhibitor (SSRI) and/or selective noradrenaline reuptake inhibitor (SNRI) were excluded. Patients who were unable to give detailed information on the occurrence of RBD or PD motor symptoms were also excluded.

2.1.3. Patient consent and standard protocol approvals

All patients provided written informed consent to participate in this study and signed additional consent forms to agree with the use of their night-time video for scientific purposes. This study was approved by our hospital's ethical committee.

2.2. Polysomnography

All participants completed an overnight video-PSG study (Compumedics-E series, Australia). The basic recordings included standard electroencephalogram (EEG; F3–A2, F4–A1, C3–A2, C4–A1, O1–A2, O2–A1), electro-oculogram (EOG; LE–A2, RE–A1), chin electromyogram (EMG), bilateral leg EMG (anterior tibialis muscles), electrocardiogram (ECG), nasal–oral pressure transducer airflow, thermal oro-nasal airflow, thoracic and abdominal respiratory efforts, oxyhemoglobin saturation, snoring sound, and body position. Awakenings, sleep stages, periodic leg movements during sleep (PLMS), and respiratory-related parameters including apnea hypopnea index (AHI), oxygen desaturation index (ODI), and percentage of time spent at oxygen saturation (SaO_2) <90% (time – [SaO_2 < 90%]), were visually scored by experienced PSG technologists and clinicians, according to American Academy of Sleep Medicine guidelines [15]. On the basis of video-PSG and clinical evaluations, a diagnosis of RBD was made according to the criteria of the International classification of sleep disorders, 2nd edition (ICSD-2) [15]. According to a previously published method, the REM sleep without atonia (RSWA) PSG criteria were either >30% of REM sleep with tonic chin EMG activity (tonic density), or >15% of REM sleep with phasic chin EMG density activity (phasic density) [16].

2.3. Clinical evaluations

Evaluations were performed at the Center of Parkinsonism and Movement Disorders. A specialist in movement disorders and sleep disease carried out a complete evaluation of each patient's disease while blinded to the PSG evaluation. Evaluations were carried out in the medication 'on' state. All participants underwent the following assessments and interviews at the time of PSG.

2.3.1. Demographics and detailed clinical history

The following information was obtained from all patients: gender, age, education, BMI, PD and RBD duration, and LED [17] at the time of PSG. Particular attention was paid to the clinical history regarding the timing of RBD and PD motor symptoms onset. Because of the relative difficulty in reconstructing the precise dates for the onset of each disease, we evaluated whether RBD clearly preceded (at least one year) the occurrence of the earliest PD symptoms to define RBD onset preceding (RBD > PD), or not (PD ⩾ PD), the onset of PD. The RBD questionnaire – Hong Kong (RBDQ-HK) [18] was used to assess RBD symptom severity for PD patients with RBD. This information was collected during clinical interviews with patients, their family, and their bed partners.

2.3.2. Motor manifestations

According to Unified PD Rating Scale (UPDRS)-based criteria developed by Schiess et al. [19], patients were divided into tremor-dominant, akinetic, and mixed subtypes. Hoehn & Yahr (H–Y) stage and all parts of UPDRS were measured. The presence of dyskinesia was assessed according to questions 32–35 of UPDRS IV. Additionally, according to location, UPDRS III was subdivided into axial (items 18, 19, 22, 27, 30) and limb (items 20–26). The ratio between the summed axial and limb scores was then calculated. The presence of falls and freezing was evaluated, according to score ⩾1 for questions 6 and 7 on UPDRS II [20].

2.3.3. Non-motor manifestations and quality of life: non-motor symptom questions (NMSQ)

These approaches were initially used to investigate the occurrence of non-motor symptoms, including olfactory dysfunction, constipation, and hallucinations. Cognition function, hypersomnia, autonomic dysfunction, and quality of life were respectively assessed with the Montreal Cognitive Assessment (MOCA, Beijing Version), Epworth Sleepiness Scale (ESS), the scale for outcomes in PD for autonomic symptoms (SCOPA-AUT), and the PD Questionnaire (PDQ).

2.4. Statistical analysis

SPSS software version 17.0 (Chicago, IL, USA) was used for the statistical analyses. Descriptive data are presented as mean ± standard deviation, median (interquartile range), or frequency (percentage). All comparisons were performed by means of analysis of covariance (ANCOVA) or Kruskal–Wallis ANOVA, for control gender, age, education, BMI, LED, and PD duration, as appropriate. Pearson's and Spearman's correlations were used to analyze the correlations between clinical manifestations with RBD duration and interval of RBD preceding PD onset. Statistical significance was defined as $P < 0.05$.

3. Results

3.1. Demographics and clinical features

In all, 120 patients with PD were investigated. Five were excluded due to technical problems during PSG and three who were unable to give detailed information on the occurrence of RBD or PD motor symptoms. Finally, 112 patients were available to participate in this study.

Of these 112 PD patients, 70 were men and 42 women with a mean age of 66.16 ± 9.33 years (range, 44–83), mean PD duration of 53.52 ± 40.67 months (range, 4–192), mean H–Y stage of 2.21 ± 0.67 (range, 1–4), and mean LED of 458.17 ± 296.25 mg/day (range, 37.5–1633.33) (Fig. 1). According to the criteria of ICSD-2 [15], 63 of 112 PD patients were affected by RBD (65.07%) and the number of PD patients in whom RBD preceded PD onset was 41 (36.60%).

The main clinical features of the two groups are summarized in Table 1. After adjustment for age, gender, education, BMI, PD duration and LED, PD + RBD patients had a higher ratio of axial/limb dysfunction (1.02 ± 0.08 vs 0.68 ± 0.52, $P = 0.003$), higher H–Y stage ($P = 0.006$), and more scores of UPDRS part I (3.71 ± 2.12 vs 2.54 ± 1.74, $P = 0.003$), II (3.71 ± 2.12 vs 2.54 ± 1.74, $P = 0.025$) and III (3.71 ± 2.12 vs 2.54 ± 1.74, $P = 0.023$), increased incidences of dyskinesia (23.80% vs 6.10%, $P = 0.018$) and hallucinations (34.92% vs 16.32%, $P = 0.033$), lower MOCA scores (23.63 ± 3.45 vs 25.06 ± 3.52, $P = 0.035$) and PDQ (138.68 ± 21.52 vs 149.56 ± 23.81, $P = 0.014$). There were no significant differences in frequencies of falling, nor in the SCOPA-AUT and ESS scores.

Table 2 shows the clinical characteristics between PD − RBD, RBD > PD and PD ⩾ RBD groups. The differences in clinical features were not statistically significant between RBD > PD and PD ⩾ RBD subgroups. However, when compared to the PD-RBD group, PD ⩾ RBD subgroup still had a significantly higher UPDRS part I score (4.45 ± 2.42 vs 2.54 ± 1.74, $P < 0.05$) and lower PDQ score (137.85 ± 22.62 vs 149.56 ± 23.81, $P < 0.05$), but not the RBD > PD subgroup.

3.2. PSG parameters

PSG parameters are shown in Table 3. When compared to PD patients without RBD, those with RBD had significantly higher percentages of tonic [13.88 (3.07–39.96) vs 4.86 (1.20–19.09), $P = 0.038$] and phasic [26.74 (14.41–39.96) vs 12.74 (6.69–19.09), $P = 0.017$] EMG activities and lower severity of oxygen desaturation during REM sleep, including less AHI, ODI, and percentage of time spent at $SaO_2 < 90\%$ during REM sleep ($P = 0.001$, 0.004, and 0.001, respectively). Significant differences in other sleep parameters, including AHI, ODI and time ($SaO_2 < 90\%$) (%) during total sleep and non-REM sleep, were not found in PD patients with and without RBD.

As shown in Table 4, the PD ⩾ RBD subgroup did not significantly differ from RBD > PD subgroup in PSG parameters. Nonetheless, the PD ⩾ RBD subgroup exhibited significantly less AHI during REM sleep [0.8 (0–5.0) vs 5 (1.2–7.9), $P < 0.05$] than the PD − RBD group, but not RBD > PD subgroup. There were no significant differences in other PSG parameters in PD + RBD and PD − RBD groups, RBD > PD and PD ⩾ RBD subgroups, such as total sleep time, sleep latency, sleep efficiency, PLMS index, the percentages of non-REM sleep 1 (NREMS1), NREMS2, REM sleep, slow-wave sleep, REM latency, awakenings, orapnea-related parameters (AHI, ODI and percentage of time spent at $SaO_2 < 90\%$) during total sleep and NREM sleep.

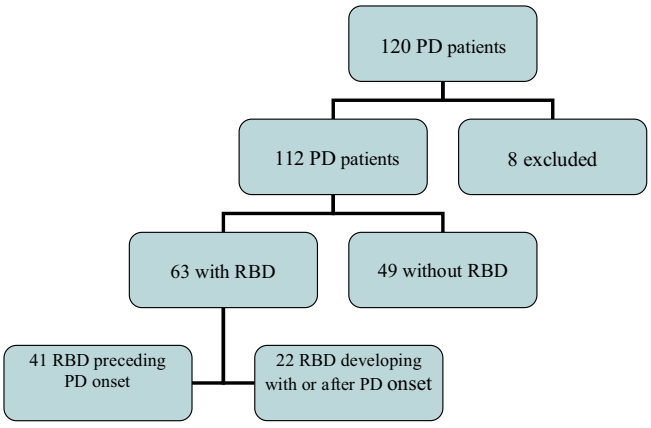

Fig. 1. Study tree of patients with Parkinson disease (PD). RBD, rapid eye movement sleep behavior disorder.

3.3. Correlation analysis

To further explore the associations of the presence of RBD with clinical manifestations, the data were subjected to correlation analysis. Table 5 shows that lower MOCA score in RBD > PD patients is significantly associated with shorter interval of RBD preceding PD onset ($r = 0.297$, $P = 0.018$), but not with RBD duration alone ($P = 0.202$). To our surprise, there were no significant correlations of RBD duration or interval of RBD preceding PD onset with other clinical variables.

4. Discussion

To our knowledge, many studies have been performed to explore the potential relationships between PD and RBD [6–10], but there have been no consistent results. Some studies found that RBD was associated with longer PD duration and higher LED in PD patients [7,10,11]. In contrast, several studies [6,9] found that there were no significant differences in markers of overall disease severity, quantitative motor testing, and motor complications between PD patients with and without RBD. A recent brief report also found that RBD in newly diagnosed, treatment-naive PD patients was not associated with motor symptom severity or cognitive decline [21]. Nonetheless, these studies did not match for disease duration and LED. A previous study suggested that disease duration and medication as disease-inherent interdependent factors could impact the macrostructure of sleep and other PSG parameters of PD [12]. In our study, by controlling age, gender, BMI, PD duration and LED, we still found that those with RBD had more severe motor and non-motor symptoms, and worse quality of life. Our findings are compatible with the hypothesis that PD patients with RBD might have more widespread and more severe of degenerative changes [22,23], including various brainstem nuclei in the pons and the medulla that modulate REM sleep. To some extent, these results may also explain why a certain proportion of PD patients does not manifest RBD.

One of the striking findings was that worse cognition was correlated with the interval of RBD onset before appearance of PD motor symptoms, but not RBD duration. This finding indicates that worse cognition may result from degenerative processes of the dopaminergic and cholinergic neurons of the brainstem nuclei, when patients with RBD develop PD motor signs in a shorter time [22]. Neuropsychological deficits observed in RBD patients may be related to the changes in cortical regions where brainstem nuclei have diffuse projections [24]. Therefore, the finding is also compatible with Braak et al.'s staging system for PD [5]. A prospective study reported that cognitive impairment could develop over time

Table 1
Demographic and clinical features in patients with Parkinson disease (PD) with (PD + RBD) and without (PD − RBD) rapid eye movement sleep behavior disorder (RBD).[a]

Demographic and clinical features	PD + RBD (n = 63)	PD − RBD (n = 49)	P-value
Male (%)	40 (63.49)	30 (61.22)	NA
Age (years)	66.84 ± 7.80	65.30 ± 11.03	NA
Body mass index (kg/m^2)	22.85 ± 3.12	22.28 ± 3.17	NA
PD duration (months)	57.05 ± 43.12	52.00 ± 37.23	NA
LED (mg/day)	509.58 ± 314.50	496.09 ± 259.23	NA
Hoehn & Yahr stage	2.5 (1–4)	2.0 (1–3)	0.006
Schiess Classification (akinetic rigid/tremor + mixed)	50/13	38/11	0.821
Ratio of axial/limb	1.02 ± 0.08	0.68 ± 0.52	0.003
UPDRS part I score	3.71 ± 2.12	2.54 ± 1.74	0.003
UPDRS part II score	12.36 ± 5.61	9.56 ± 5.28	0.025
UPDRS part III score	22.50 ± 9.83	18.26 ± 9.45	0.023
Dyskinesia, n (%)	15 (23.80)	3 (6.10)	0.018
Falling, n (%)	17 (26.98)	7 (14.28)	0.163
Freezing, n (%)	28 (55.56)	21 (42.85)	0.247
Olfactory dysfunction, n (%)	24 (38.09)	15 (30.61)	0.432
Constipation, n (%)	45 (71.43)	33 (67.34)	0.682
Hallucinations, n (%)	22 (34.92)	8 (16.32)	0.033
SCOPA-AUT score	10.36 ± 5.87	9.42 ± 6.22	0.427
ESS score	8.047 ± 4.47	7.14 ± 3.97	0.272
MOCA score	23.63 ± 3.45	25.06 ± 3.52	0.035
PDQ score	138.68 ± 21.52	149.56 ± 23.81	0.014

NA, not applicable; LED, levodopa equivalent daily dose; UPDRS, Unified Parkinson's Disease Rating Scale; SCOPA-AUT, scale for outcomes in PD for autonomic symptoms; ESS, Epworth Sleepiness Scale; MOCA, Montreal cognitive function monitoring scale; PDQ, quality-of-life questionnaire.
Values are mean ± standard deviation, or frequencies (percentage), or median (interquartile range).
[a] Adjusted for age, gender, education, body mass index, PD duration, and LED.

Table 2
Clinical manifestations in Parkinson disease (PD) patients without RBD (PD − RBD), RBD preceding PD onset (RBD > PD), and RBD developing with or after (PD ⩾ RBD) PD onset.[a]

Clinical manifestations	RBD > PD (n = 22)	PD ⩾ RBD (n = 41)	PD − RBD (n = 49)
Gender male (%)	29 (70.73)	11 (50)	30 (61.22)
Age (years)	66.93 ± 8.33	66.68 ± 6.88	65.30 ± 11.03
Body mass index (kg/m^2)	22.23 ± 3.15	22.37 ± 3.28	22.28 ± 3.17
PD duration (months)	50.49 ± 39.08	58.86 ± 45.48	52.00 ± 37.23
LED (mg/day)	467.22 ± 296.11	518.50 ± 339.32	496.09 ± 259.23
RBD duration (months)	171.60 ± 15.65	30.37 ± 21.69[b]	–
ESS score	8.29 ± 0.72	7.58 ± 0.99	7.14 ± 3.97
MOCA score	23.85 ± 3.34[d]	23.23 ± 3.70[c]	25.06 ± 3.52
SCOPA-AUT score	11.00 ± 5.72	9.18 ± 6.08	9.42 ± 6.22
Hallucinations, n (%)	16 (39.02)	6 (27.27)	15 (30.61)
Hoehn & Yahr stage	2.38 ± 0.62[d]	2.41 ± 0.71[c]	2.0 (1–3)
Scheiss classification (akinetic rigid/tremor + mixed)	23/18	14/8	38/11
Ratio of axial/limb	1.19 ± 1.81	0.89 ± 0.48	0.68 ± 0.52
UPDRS part I score	3.61 ± 1.96	4.45 ± 2.42[c]	2.54 ± 1.74
UPDRS part II score	11.88 ± 5.38	14.32 ± 6.76	9.56 ± 5.28
UPDRS part III score	24.36 ± 13.84	31.71 ± 17.16	18.26 ± 9.45
Dyskinesia, n (%)	13 (31.70)	8 (36.36)	3 (6.10)
Falling, n (%)	11 (26.82)	6 (27.27)	7 (14.28)
PDQ	140.23 ± 19.73	137.85 ± 22.62[c]	149.56 ± 23.81
RBDQ-HK score	44.32 ± 18.92	41.86 ± 18.12	–
RBDQ-HK (factor 1)	13.93 ± 6.78	14.36 ± 5.71	–
RBDQ-HK (factor 2)	30.46 ± 13.89	27.55 ± 14.00	–

RBD, rapid eye movement (REM) sleep behavior disorder; LED, levodopa equivalent daily dose; ESS, Epworth Sleepiness Scale; MOCA, Montreal cognitive function monitoring scale; SCOPA-AUT, the scale for outcomes in PD for autonomic symptoms; UPDRS, Unified Parkinson's Disease Rating Scale; PDQ, quality-of-life questionnaire; RBDQ-HK, RBD questionnaire – Hong Kong.
Values are mean ± standard deviation or frequencies (percentage).
[a] Adjusted for age, gender, education, body mass index, PD duration and LED.
[b] Significant between PD ⩾ RBD and RBD > PD.
[c] Significant between PD ⩾ RBD and PD − RBD.
[d] Significant between RBD > PD and PD − RBD.

in RBD patients and that a significant deterioration in visuo-spatial functions was observed after a mean period of approximately two years [25]. However, that study [25] found that cognitive dysfunction did not predict the development of PD motor signs, which would contrast with our finding. The author explained that cell loss in the substantia nigra would still occur earlier than in cortical areas, but perhaps progressing at a slower rate. Another may be that the follow-up period (26.3 ± 5.0 months) was not enough to find that cognitive dysfunction would predict the development of PD motor signs in this study. There was significant correlation between cognition and the interval of RBD before PD onset, but this significance observed in our study was not very high. It remains to

Table 3
Polysomnographic measurements of sleep parameters in Parkinson disease (PD) patients with (PD + RBD) and without (PD − RBD) RBD.[a]

Sleep parameters	PD + RBD (n = 63)	PD − RBD (n = 49)	P-value
TST (min)	334.22 ± 103.93	314.88 ± 143.38	0.410
SE (%)	61.21 ± 18.44	60.49 ± 22.69	0.854
SL (min)	32.46 ± 46.32	36.78 ± 62.41	0.675
Awakenings (n)	20.49 ± 10.06	21.37 ± 12.17	0.676
NREMS1 (min)	110.99 ± 76.14	91.01 ± 56.80	0.128
NREMS1 (%)	33.60 ± 21.07	32.21 ± 17.44	0.709
NREMS2 (min)	136.30 ± 71.51	139.11 ± 72.41	0.838
NREMS2 (%)	40.50 ± 16.51	43.57 ± 14.57	0.850
SWS (%)	12.05 ± 10.76	11.63 ± 12.27	0.852
REML (min)	146.30 ± 95.94	144.08 ± 93.61	0.790
REMS (min)	146.30 ± 95.94	144.08 ± 93.60	0.903
REMS (%)	13.86 ± 8.59	16.28 ± 21.10	0.409
AHI (/h) during NREMS	1.1 (0.1–4.7)	1.3 (0–6.7)	0.668
AHI (/h) during REMS	0.9 (0–4.7)	5 (1.2–7.9)	0.001
AHI (/h) during sleep	0.8 (0–4.9)	1.5 (0–7.9)	0.289
ODI (/h) during NREMS	1.5 (0.5–4.2)	0.7 (0.1–6.5)	0.408
ODI (/h) during REMS	0.9 (0.3–2.8)	2.3 (0.6–8.0)	0.004
ODI (/h) during sleep	1.1 (0.3–4.3)	1.0 (0.2–7.1)	0.726
Time (SaO_2 < 90%) (%) during NREMS	0.1 (0–0.3)	0.0 (0–0.8)	0.182
Time (SaO_2 < 90%) (%) during REMS	0.1 (0–4.0)	0.7 (0–4.0)	0.001
Time (SaO_2 < 90%) (%) during sleep	0.0 (0–0.2)	0.0 (0–1.1)	0.406
PLMSI (/h)	10.5 (3.30–43.6)	5.5 (0–34.9)	0.116
Tonic EMG activity (%)	13.88 (3.07–39.96)	4.86 (1.20–19.09)	0.038
Phasic EMG activity (%)	26.74 (14.41–39.96)	12.74 (6.69–19.09)	0.017

RBD, rapid eye movement (REM) sleep behavior disorder; TST, total sleep time; SE, sleep efficiency; SL, sleep latency; NREMS, non-rapid eye movement sleep; SWS, slow wave sleep; REML, rapid eye movement latency; REMS, rapid eye movement sleep; AHI, apnea–hypopnea index; ODI, oxygen desaturation index; SaO_2, arterial oxygen saturation; PLMSI, index of periodic leg movements during sleep; EMG, electromyogram.
Values are mean ± standard deviation, or median (interquartile range).
[a] Adjusted for age, gender, education, body mass index, PD duration and levodopa equivalent daily dose.

Table 4
Polysomnographic measurements of sleep parameters in Parkinson disease (PD) patients without RBD (PD − RBD), RBD preceding PD onset (RBD > PD), and RBD developing with or after PD onset (PD ⩾ RBD).[a]

Sleep parameters	RBD > PD (n = 22)	PD ⩾ RBD (n = 41)	PD − RBD (n = 49)
TST (min)	340.69 ± 106.78	322.15 ± 99.70	314.88 ± 143.38
SE (%)	61.41 ± 18.47	60.84 ± 18.83	60.49 ± 22.69
SL (min)	33.39 ± 49.77	30.73 ± 40.14	36.78 ± 62.41
Awakenings (n)	19.71 ± 9.88	21.95 ± 10.45	21.37 ± 12.17
NREMS1 (min)	117.41 ± 80.25	99.02 ± 67.94	91.01 ± 56.80
NREMS1 (%)	34.24 ± 21.94	32.41 ± 19.79	32.21 ± 17.44
NREMS2 (min)	132.31 ± 68.00	143.75 ± 78.73	139.11 ± 72.41
NREMS2 (%)	39.11 ± 16.20	43.07 ± 17.16	43.57 ± 14.57
SWS (%)	11.21 ± 10.54	13.61 ± 11.23	11.63 ± 12.27
REML (min)	147.06 ± 90.74	144.89 ± 107.19	144.08 ± 93.61
REMS (min)	53.73 ± 34.90	38.82 ± 29.52	144.08 ± 93.60
REMS (%)	15.47 ± 8.70	10.87 ± 7.70	16.28 ± 21.10
AHI (/h) during NREMS	1.0 (0.1–5.0)	1.2 (0.1–4.8)	1.3 (0–6.7)
AHI (/h) during REMS	1.0 (0–4.6)	0.8 (0–5.0)	5 (1.2–7.9)[b]
AHI (/h) during sleep	0.8 (0–5.0)	1.0 (0 –4.9)	1.5 (0–7.9)
ODI (/h) during NREMS	1.3 (0.3–4.6)	1.6 (0.7–4.0)	0.7 (0.1–6.5)
ODI (/h) during REMS	1.1 (0.2–2.9)	0.6 (0.4–2.7)	2.3 (0.6–8.0)[b,c]
ODI (/h) during sleep	1.1 (0.3–4.8)	1.1 (0.2–4.1)	1.0 (0.2–7.1)
Time (SaO_2 < 90%) (%) during NREMS	0.2 (0–0.3)	0.1 (0–0.3)	0.0 (0–0.8)
Time (SaO_2 < 90%) (%) during REMS	0.1 (0–0.5)	0.1 (0–0.3)	0.7 (0–4.0)[b,c]
Time (SaO_2 < 90%) (%) during sleep	0.0 (0–0.2)	0 (0–0.15)	0.0 (0–1.1)
PLMSI (/h) 12.3 (3.3–47.2)	7.0 (3.2–43.2)	5.5 (0–34.9)	
Tonic EMG activity (%)	13.4 (6.3–33.7)	13.8 (1.8–69.0)	4.86 (1.20–19.09)[b,c]
Phasic EMG activity	(%) 26.7 (15.8–48.9)	29.7 (13.6–56.9)	12.74 (6.69–19.09)[b,c]

RBD, rapid eye movement (REM) sleep behavior disorder; TST, total sleep time; SE, sleep efficiency; SL, sleep latency; NREMS, non-rapid eye movement sleep; SWS, slow wave sleep; REML, rapid eye movement latency; REMS, rapid eye movement sleep; AHI, apnea–hypopnea index; ODI, oxygen desaturation index; SaO_2, arterial oxygen saturation; PLMSI, index of periodic leg movements during sleep; EMG, electromyogram.
Values are mean ± standard deviation, or frequencies (percentage), or median (interquartile range).
[a] Adjusted for age, gender, education, BMI, PD duration and levodopa equivalent daily dose.
[b] Significant difference between PD ⩾ RBD and PD − RBD.
[c] Significant difference between RBD > PD and PD − RBD.

be ascertained whether neuropsychological impairment is an early marker of an ongoing neurodegenerative process. Therefore, more prospective studies with a longer follow-up period are needed to confirm our finding and explore potential relationships between cognition and the interval of RBD onset before appearance of PD motor symptoms.

Table 5
Correlation analysis of clinical manifestations with RBD duration and interval of RBD before PD onset.

Clinical manifestations	RBD duration		Interval of RBD before PD onset	
	r	*P*-value	*r*	*P*-value
Hoehn & Yahr stage[a]	0.071	0.579	−0.078	0.542
UPDRS I score	0.032	0.802	−0.042	0.746
UPDRS II score	0.029	0.820	−0.053	0.682
UPDRS III score	0.030	0.838	−0.035	0.835
Ratio of axial/limb	0.010	0.940	0.074	0.851
LED	0.059	0.643	−0.168	0.188
MOCA score	0.163	0.202	0.297	0.018
PDQ score	−0.167	0.191	0.176	0.167
RBD-HK score	0.078	0.541	0.103	0.421
SCOPA-AUT score	0.029	0.821	0.135	0.290
TST	0.028	0.827	0.093	0.467
SE (%)	0.024	0.852	0.096	0.452
SL (min)	−0.052	0.687	0.132	0.304
REML (min)	0.095	0.457	−0.108	0.398
Awakenings (*n*)	0.215	0.091	0.217	0.088
NREMS1 (%)	0.221	0.082	0.119	0.355
NREMS2 (%)	−0.109	0.395	−0.058	0.654
SWS (%)	−0.237	0.067	−0.159	0.212
REMS%	0.036	0.777	0.019	0.885
AHI (/h) during REMS[a]	−0.078	0.545	0.045	0.727
ODI (/h) during REMS[a]	−0.125	0.330	0.118	0.358
Time (SaO_2 < 90%) (%) during REMS[a]	−0.002	0.990	0.026	0.837
PLMSI[a]	0.054	0.672	0.083	0.520

RBD, rapid eye movement (REM) sleep behavior disorder; PD, Parkinson disease; UPDRS, Unified Parkinson's Disease Rating Scale; LED, levodopa equivalent daily dose; MOCA, Montreal cognitive function monitoring scale; PDQ, quality-of-life questionnaire; RBD-HK, RBD questionnaire – Hong Kong; SCOPA-AUT, the scale for outcomes in PD for autonomic symptoms; TST, total sleep time; SE, sleep efficiency; SL, sleep latency; REML, NREMS1, non-REM stage 1; SWS, slow wave sleep; REMS, rapid eye movement sleep; AHI, apnea–hypopnea index; ODI, oxygen desaturation index; SaO_2, oxygen saturation; REMS, rapid eye movement sleep; PLMSI, index of periodic leg movements during sleep.
Interval of RBD before PD onset = the time from RBD onset to the onset of PD motor symptoms.
[a] Spearman correlation.

Another interesting finding was that PD patients with RBD had lower severity of oxygen desaturation during REM sleep than those without RBD, whereas this finding did not exist during total sleep and NREM sleep. This indicates that RBD would protect PD patients against severe obstructive sleep apnea (OSA), in view of the typical feature of persistent EMG activity during REM sleep. The possible explanations were as follows. First, it has been proposed since the 1990s that RBD is protective against OSA [26]. Decreased muscle tone of pharyngeal airway dilator muscles plays a critical role in the pathogenesis of OSA [27,28]. Moreover, studies of animal models and human subjects confirmed that tonic and phasic EMG activities of pharyngeal airway dilator muscles gradually decrease from wakefulness, NREM to REM sleep [28–30]. So the reduction of upper airway dilator muscle EMG activity could contribute to the increased severity of OSA during normal REM sleep. Second, peak and tonic EMG activity in upper airway dilator muscle, which is partially determined by EMG activity during REM sleep, has been shown to be associated with stable breathing [30]. Finally, one study also found that PD patients who were accompanied by increased muscle tone during REM sleep had lower severity of OSA than controls [31]. Moreover, a recent case–control study suggested that RBD may be a naturalistic model for understanding neuromuscular control of OSA [32].

An unexpected but interesting finding was that two subgroups all exhibited significantly greater severity of disease, worse cognition, and lower severity of oxygen desaturation than the PD − RBD group, whereas the PD ⩾ RBD subgroup did not significantly differ from the RBD > PD subgroup in clinical manifestations. In contrast, Ferri et al. [13] reported that RBD > PD patients (n = 6) did not differ from PD − RBD patients in clinical variables, whereas PD ⩾ RBD patients (n = 10) exhibited significantly greater severity of PD than RBD > PD patients. One possible reason was the unified criteria of the time of RBD preceding PD onset. The definition of time of RBD preceding the occurrence of the earliest PD symptom was at least one year in our study, whereas RBD clearly preceded (by at least six months) PD symptom onset in Ferri et al.'s study. Another possible reason was the different severity of PD at baseline. In our study, PD patients overall had more severity of PD than those in Ferri et al.'s study, such as higher H–Y stage and longer PD duration. On the other hand, Ferri et al.'s study did not match for H–Y stage, PD duration, and LED to compare other clinical variables, which may also have contributed to the different results. At present, it is still unclear whether timing of RBD onset may indicate different disease courses and different underlying temporal sequences of pathology of PD. The timing of RBD onset in relation to PD is an important parameter to be included in future studies. We would try to explore the specific clinical implications of timing of RBD onset in prospective studies by expanding the sample.

The major limitation of this study is that it was retrospective and only included a single evaluation time-point. The samples of RBD > PD and PD ⩾ RBD may not be large enough to detect differences in clinical manifestations.

5. Conclusions

Our results show that clinical manifestations of PD could vary depending on the presence of RBD and the timing of RBD onset. These findings are compatible with the hypothesis that RBD may be a marker of complex subtypes of PD and that PD might constitute distinct clinical and pathological subtypes related to the presence and/or timing of RBD onset.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.12.021.

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